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VINCRISTINE AND VINBLASTINE: A REVIEW

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ABSTRACT

Vincristine and vinblastine are originally derived from the periwinkle plant Catharanthus roseus . Vincristine and vinblastine act as inhibitors during the metaphase of the cell cycle and by binding to the microtubules inhibit the development of the mitotic spindle.

KEYWORDS: Madagascar Periwinkle, Vincristine, Vinblastine, Tubulin, Cell Division

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Original Article

INTRODUCTION

It's from the pink periwinkle plant, Catharanthus roseus G. Don, Vinca alkaloids are naturally extracted. The vinca alkaloids are important for being anticancer drugs like vincristine and vinblastine.

The productivity of vinblastine and vincristine is very low in plants (0.001-0.0003%) resulting in their extraordinary high price. Vinblastine is a dimeric indole alkaloid and is formed by coupling of vindoline and catharanthine catalysed by horseradish peroxidase[1]. The yield of coupling products, (15' 20'- anhydro vinblastine) was reported very low (0.9%). Vinblastine is converted into vincristine by the oxidation of its methyl group. Most of the key enzymes of the indole alkaloid biosynthetic pathway have been isolated from seedlings and / or cell suspension cultures of the *C. roseus* [2]. The cell cultures do not produce dimeric and monomeric indole alkaloids but catharanthine is produced in considerable amounts. Vincristine, vinblastine and vindoline were reported only in shoot cultures and differentiated tissues but not in roots[3,4]. Recently a stable, high producing and salt tolerant cell lines of *C. roseus* plant has been developed to achieve industrial production of the alkaloids.

The major limitation of these drugs in cell cultures is their low yield. Particularly the improvement of catharanthine production in *C. roseus* cell cultures is of great interests for pharmacologists and chemists because catharanthine and vindoline can be coupled to form vinblastine in high yield, and vindoline is abundant in plants[5]. Elicitors can also modulate the production of these alkaloids as reported by Moreno *et al.* in 1981[6]. Involvement of metabolic engineering for alternative production methods was encouraged and made possible due to low vinblastine and vincristine contents in the plants[3,7]. Engineering techniques like semisynthesis[8], total chemical synthesis or even of chemical[11,12] or enzymatic coupling [13]of commercially available catharanthine and vindoline is useful[9,10].

Clinical Pharmacology

Vincristine

Pharmacokinetic studies of vincristine are limited by a lack of sensitive assays for measuring plasma concentrations of vincristine. Plasma clearance is rapid owing to extensive tissue binding and large volume of

distribution. Vincristine is thought to have tri-exponential pharmacokinetics with rapid distribution following bolus injection, β phase distribution of 50–155 min, and an elimination half-life of approx 85 h [14-18].

Children appear to have higher plasma clearance than adults. Vincristine is metabolized in the liver by cytochrome P450 3A, and concomitantly administered drugs may either competitively inhibit or induce cytochrome P450 3A clearance of vincristine [19, 20].

Vincristine accumulates in many tissues such as the lung, liver, kidney, bone marrow, intestinal mucosa, pancreas, and spleen. It is largely excluded from the brain, eye, and adipose tissue [21]. Vincristine is excreted as either unchanged drug or as a metabolite in the bile and feces[22]. Vincristine has little renal excretion. The relationship between the plasma pharmacokinetics and antitumor effects of vincristine is not fully defined.

Vincristine is typically administered as a bolus intravenous infusion at 1.4 mg/m^2 in adults (maximum dose of 2 mg), and at 1.5–2.0 mg/m^2 in children (maximum dose of 2.0–2.5 mg). Vincristine may be given up to once weekly, however, the dosing schedule varies based upon the malignancy, response, and other concomitantly administered drugs. Neurotoxicity is the dose-limiting toxicity, and attempts to use continuous infusion instead of bolus injection to reduce neurotoxicity have been inconclusive [23, 24]. The dose of vincristine is reduced in the setting of severe hepatic dysfunction or severe neurotoxicity. Typically patients will receive 50% of the planned dose for moderate hyperbilirubinemia, and 25% for severe hyperbilirubinemia[25].

Vinblastine

Pharmacokinetic studies of patients treated with a bolus injection of vinblastine are consistent with a triexponential pharmacokinetic model, similar to vincristine.

Vinblastine is rapidly distributed from the plasma to tissues, primarily to the lung, liver, spleen, and kidneys. The elimination half-life of vinblastine is approx 29 h, with very little drug remaining in the body at 48 h [26, 27]. Similar to the other vinca alkaloids, vinblastine is metabolized by the hepatic cytochrome P450 3A enzyme. This pathway may be impaired in patients with hepatic dysfunction and may be affected by other medications, which either induce or inhibit the activity of cytochrome P450 3A.

Vinblastine is largely excreted in the bile and feces, with little renal excretion [27]. The dose of vinblastine in children and adults is typically 6 mg/m^2, with modifications for hepatic dysfunction and hematological tolerance.

Side Effects

Vincristine

Neurotoxicity is the dose-limiting side effect of vincristine. Vincristine-induced neuropathy is a cumulative toxicity; however, some symptoms develop within the first few weeks of treatment. Initial neurotoxic signs and symptoms include symmetrical sensory impairment and parasthesias. Patients may later have loss of deep tendon reflexes, develop gross motor abnormalities such as foot or wrist drop, or experience a decrease in fine motor skills such as writing. Autonomic polyneuropathy is seen in some patients, manifested by constipation, paralytic ileus, bladder dysfunction, and impotency. Many of the symptoms resolve within weeks to months of discontinuation of therapy, however residual neurotoxicity has been documented[23, 24]. The severity of neurotoxicity may be influenced by the dosage and frequency of administration. Doses of vincristine are typically capped at 2 mg or 2.5 mg because of concerns that autonomic

neurotoxicity is more affected by the size of a single dose rather than cumulative dose [24, 28, 29]. Vincristine-induced neurotoxicity is greatest in infants and the elderly and may be related to dose calculations. A correlation between neurotoxicity and obstructive liver disease has also been shown, to result in impaired biliary excretion of vincristine [29].

Concomitant administration of radiation therapy or chemotherapeutic agents such as L- aspariginase may also worsen the neurotoxicity associated with vincristine[30]. Of note, severe central nervous system toxicity has been reported in patients who were given high doses or who have a disrupted blood brain barrier. Intrathecal administration of vincristine is almost always fatal, and therefore this must be carefully avoided [31]. In addition to neurotoxicity, patients will experience mild neutropenia and anemia following administration of vincristine. This is readily reversible and does not usually result in treatment delay [32]. The development of alopecia and rash following vincristine is variable depending upon the dose and duration of treatment. Common gastrointestinal side effects include constipation, abdominal cramping, nausea and vomiting. Patients may also complain of urinary symptoms secondary to polyuria, dysuria, or bladder rentention[33].

Vinblastine

Myelosuppression is the dose-limiting toxicity of vinblastine. Neutropenia is the most common manifestation of myelosuppression, with anemia and thrombocytopenia being less frequent. Neutropenia occurs approximately 4–10 days following administration of the drug, and counts usually recover within 7–21 days of administration. Neurotoxicity is less common with vinblastine than with vincristine, and usually occurs after prolonged administration or in combination regimens[34, 35]. Patients may complain of gastrointestinal side effects such as mucositis and stomatitis; nausea and vomiting may occur but are less common. Mild alopecia is seen and is reversible. There are case reports of acute hypertension and pulmonary edema, but these are infrequent side effects of vinblastine.

The medicinal plant Catharanthus roseus contains large number of terpenoid indole alkaloid (TIAs) with over 70 compounds isolated and identified. Thus there exists a large demand for these anticancer alkaloids. Yield of 50 grams of crude vincristine sulphate is made possible from one tone of *Catharanthus roseus* leaves.

Low Yield in Process

Vincristine, the antileukaemia drug which is in demand, suffers from the disadvantage of very low yields from the source material, and so is prohibitively expensive. Vinblastine, another anticancer drug from the same plant is present at levels 1000 times higher than vincristine and its cost is one third as that of vincristine. Vinblastine is now being used as the parent drug to obtain, through structural modifications, the prodrug vincristine[7].

Table 1: Chemical Data of Vinblastine

Formula	$C_{46}H_{58}N_4O_9$
Mol. mass	810.974 g/mol

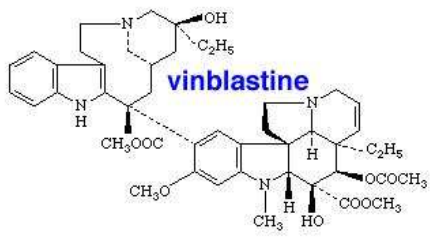

Figure 1

Table 2: Pharmacokinetic Data of Vinblastine

Metabolism	Hepatic(CYP3A4- Mediated)
Half life	24.8hours (terminal)
Excretion	Biliary and renal

History

Robert Noble and Charles Thomas Beer were the first scientist duo who first isolated Vinblastine from the Madagascar periwinkle plant. As a chemotherapeutic agent ,vinblastine was first discovered to judge its utility it was crushed into a tea.

Vincristine

Table 3: Chemical Data of Vincristine

Formula	$C_{46}H_{56}N_4O_{10}$
Mol. mass	824.958 g/mol

Figure 2

Table 4: Pharmacokinetic Data of Vincristine

Metabolism	Hepatic
Half life	19 to 155 hours
Excretion	Mostly Biliary and 10% renal

History

Studies in the 1950s report that C. roseus contained more than 100 alkaloids, due to which they are being used as a folk remedy for centuries.

Mode of Action of Vinblastine and Vincristine

Among the many biochemical effects seen after exposure of cells and tissues to the *Vinca* alkaloids are disruption of microtubules, inhibition of synthesis of proteins and nucleic acids, elevation of oxidized glutathione, alteration of lipid metabolism and the lipid content of membranes, elevation of cyclic adenosine monophosphate (cAMP) and inhibition of calcium-calmodulin regulated cAMP phosphodiesterase. The *Vinca* alkaloids are relatively hydrophobic molecules that partition into lipid bilayers in the uncharged state, altering the structure and function of membranes. Of their diverse effects, their only well-documented direct action is disruption of microtubules, which results from their reversible binding to tubulin (William *et al*, 1994).(The subunit protein of microtubules). Vinca alkaloids are pharmacologically active at most of the concentrations and biochemical effects associated with exposure to the *Vinca* alkaloids is probably secondary to disruption of microtubules, although it is possible that drug-induced changes in lipid bilayers may alter some membrane-

dependent processes. At high intracellular concentrations, these compounds induce formation of large crystalline aggregates that are composed of tubulin and drug. Despite their many biochemical actions, the antineoplastic activity of the *Vinca* alkaloids is usually attributed to their ability to disrupt microtubules, causing dissolution of mitotic spindles and metaphase arrest in dividing cells. Microtubules are involved in many cellular processes besides mitosis, and exposure to *Vinca* alkaloids give rise to diverse biologic effects, many of which could impair essential functions, both in dividing and in non dividing cells. Morphological changes and cell death after treatment with vinblastine and vincristine have been seen in non dividing normal as well as leukemic lymphocytes and also in cultured leukemic cells during interphase and in G1 and S-phase cells. Chemotaxis in human monocytes and directional migration of cultured tumor cells are inhibited by vinca alkaloids. Microtubules are required for the transport of various metabolites and the movement of organelles, including mitochondria and secretory granules, along neuronal processes. Exposure of nervous tissue to vinca alkaloids inhibits axonal transport, causing neurotoxicity. The vinca alkaloids also inhibit secretory processes, apparently as a result of perturbations in membrane trafficking with disruption of the cytoskeleton. Platelets, which depend on the integrity of the peripheral ring of microtubules for their discoidal shape, become spherical after treatment with vinca alkaloids. These few examples illustrate that the vinca alkaloids exert a variety of potentially cytotoxic effects that are unrelated to mitotic inhibition.

Although the effects of the vinca alkaloids on the organization and function of microtubules have been extensively characterized, establishing the nature and number of vinca alkaloid binding sites on tubulin has been difficult because of methodological problems, However, it appears that each heterodimer of tubulin possesses a single “vinca-specific” site of high intrinsic affinity and an unknown number of nonspecific sites of low affinity. Attempts to compare the tubulin-binding capabilities of different vinca alkaloids are also complicated by differences in assay conditions and methods of analysis of ligand-binding data. Nevertheless, some generalizations can be made.[38]

Fungi are one of the major sources of natural bioactive molecules. Over 4000 bioactive metabolites of fungal origin have been described. Plant-associated fungi in some cases are able to make the same bioactive compounds as the host plant itself. After the discovery of gibberellins from *Fusarium fujikuroi*, suggesting the possibility of intergeneric genetic exchange between plant and fungus. Endophytic fungi, associated with *Taxus brevifolia*, may produce Taxol and was confirmed by Strobel *et al* (1993) was the observation and led to the new prospect. Thus the success of finding fungal taxol prompted us to isolate endophytic fungi from *Catharanthus roseus* to produce low volume and high valued drugs, vinblastine and vincristine. Potentially, a fungal source would reduce the price of the above life-saving drugs and also save the plant from extinction in some areas.

According to the discovery by Kharwar *et al.*, [39] Zahng *et al.* [40] and Tung *et al.* [41] who isolation of several endophytic fungi from *Catharanthus roseus was conformed.* Ahmad *et al* have identified fungal (endophytic) strains which produce vinblastine and vincristine, purified with TLC, HPLC and characterized by UV-VIS, ESI-MS and ^{1}H NMR. [42,43,44]

CONCLUSIONS

The vincristine and vinblastine are anticancer drugs that act by binding to intracellular tubulin. In tumor cells, vincristine and vinblastine inhibit the DNA repair and the RNA synthesis mechanisms, blocking the DNA-dependent RNA polymerase.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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